

Adverse Effects of Vaccines Evidence and Causality

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Charge to the Committee

Review the epidemiologic, clinical, and biological evidence regarding the adverse health events associated with specific vaccines covered by VICP.

HRSA presented a list of specific adverse events for the committee to consider.

We were not asked to assess efficacy or benefits of vaccines to individuals or the population at large.

Vaccines

Measles, mumps, and rubella vaccines (MMR)

Varicella zoster vaccine

Influenza vaccines (except 2009 H1N1)

Hepatitis A vaccine

Hepatitis B vaccine

Human papillomavirus vaccine (HPV)

Tetanus-containing vaccines other than those containing the whole cell pertussis component (DT,TT,aP)

Meningococcal vaccine

Committee Membership and Process

15 member with expertise in pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law.

The committee met 8 times, including three open sessions.

The committee added 10 vaccine-adverse events to the list

All conclusions represent the consensus of the entire committee.

Evidence Review

Medical librarian conducted 3 comprehensive searches and spot searches. Search terms are in Appendix C.

Peer reviewed literature (no abstracts, unpublished data)

Original research only

General Framework for Causation

Epidemiologic weight of evidence (four categories; 2 have a “direction” of increased risk, decreased risk, or null)

Mechanistic (biological and clinical) weight of evidence (four categories; can only be used to “support” causation)

Causality conclusions (4 categories)

Weighing epidemiologic evidence

Methodologic issues:

- A priori definition of exposure

- Verification of vaccine administration and adverse event

- Control of confounding and bias

- Adequacy of follow-up

- Development and use of eligibility criteria

Precision, validity, and consistency of reported results ➔

Confidence

Weight of Epidemiologic Evidence

High: *Two or more* studies with *negligible* methodological limitations that are *consistent* in terms of the direction of the effect and taken together provide high confidence.

Moderate: *One* study with *negligible* methodological limitations, *or a collection* of studies *generally consistent* in terms of the direction of the effect, provides moderate confidence.

Limited: One study or a collection of studies *lacking precision or consistency* provides limited, or low, confidence.

Insufficient: No epidemiologic studies of *sufficient* quality found.

Evaluating biological mechanisms

- Direct infection; persistent infection; reactivation
- Immune mediated mechanisms
 - T-cell
 - Antibodies and autoantibodies
 - Complement activation
 - Hypersensitivity reactions
 - Immune complexes
- Tissue responses
 - Fevers and seizures
 - Molecular mimicry
 - Antigen persistence
 - Epitope spreading
 - Bystander activation/Autoreactivity
 - Increased cytokines
 - Superantigens
- Injection related
- Coagulation

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Important attributes of case reports

Necessary but not sufficient: confirmation of vaccine administration, clinician diagnosed health outcome, appropriate temporality

Additional information: rechallenge, exclusion of other likely causes, clinical information in workup, confirmation of vaccine-strain virus

Animal and *in vitro* studies made some contribution.

Similarities to effects of natural infection alone gets evidence out of lacking and into weak.

Weight of Mechanistic Evidence

Strong: One or more cases in the literature, for which the committee concludes the vaccine was a contributing cause of the adverse event, based on an *overall assessment of attribution* in the available cases **and** *clinical, diagnostic, or experimental evidence* consistent with relevant biological response to vaccine.

Weight of Mechanistic Evidence, cont.

Intermediate: At least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.

On occasion, the committee determined that at least two cases, taken together, while *suggestive*, are nonetheless insufficient for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. This evidence has been identified in the text as “**low-intermediate.**”

Weight of Mechanistic Evidence, cont.

Weak: Insufficient evidence from cases in the literature for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.

Lacking evidence of a biologic mechanism: No clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine, regardless of the presence of individual cases in the literature.

Causality Conclusions

Evidence convincingly supports a causal relationship.

Evidence favors acceptance of a causal relationship.

Evidence is inadequate to accept or reject a causal relationship.

Evidence favors rejection of a causal relationship.

Evidence that Determined the Causality Conclusions

EPIDEMIOLOGIC ASSESSMENT						MECHANISTIC ASSESSMENT					CAUSALITY CONCLUSION			
High (increased)	High (null/decreased)	Moderate (increased)	Moderate (null/decreased)	Limited	Insufficient	Strong	Inter-mediate	Low-Inter-mediate	Weak	Lacking	Inadequate to Accept or Reject	Favors Rejection	Favors Acceptance	Convincingly Supports
High (increased)														Convincingly Supports
						Strong								
		Moderate (increased)												Favors Acceptance
							Inter-mediate							
	High (null/decreased)*												Favors Rejection	
			Moderate (null/decreased), Limited, or Insufficient**											Inadequate to Accept or Reject
								Low-Intermediate, Weak, or Lacking***						

* Causality conclusion is favors rejection only if mechanistic assessment is *not* strong or intermediate.

** Causality conclusion is inadequate to accept or reject only if mechanistic assessment is *not* strong or intermediate.

*** Causality conclusion is inadequate to accept or reject only if epidemiologic assessment is *not* high (increased), high (null/decreased), or moderate (increased).

Inadequate to accept or reject causation? What does that mean?

Some might interpret that to mean either of the following statements:

- Because the committee did not find convincing evidence that the vaccine *does* cause the adverse event, the vaccine is safe.

OR

- Because the committee did not find convincing evidence that the vaccine does *not* cause the adverse event, the vaccine is unsafe.

Neither of these interpretations is correct. “Inadequate to accept or reject” means just that—inadequate.

Inadequate to accept or reject causation? A caveat

If there is evidence in either direction that is *suggestive but not sufficiently strong* about the causal relationship, it will be reflected in the *weight-of-evidence assessments* of the epidemiologic or the mechanistic data.

However *suggestive* those assessments might be, in the end the committee concluded that the evidence was inadequate to accept or reject a causal association.

Convincingly Supports (14 Vx-AE)

Varicella: Disseminated Oka VZV without other organ involvement; Disseminated with pneumonia, meningitis, or hepatitis; Reactivation; Reactivation with meningitis or encephalitis

MMR: Febrile Seizures; Measles Inclusion Body Encephalitis (immunoincompetent only)

Anaphylaxis: MMR; Varicella; Influenza; Hepatitis B; TT; Meningococcal

Injection-related: Deltoid bursitis; Syncope

Favors Acceptance (4 Vx-AE)

HPV: Anaphylaxis

MMR: Transient arthralgia in women and in children

Influenza: OculoRespiratory Syndrome

Favors Rejection (5 Vx-AE)

MMR: Autism; Type I diabetes

DT,TT, aP: Type 1 diabetes

Influenza: Bell's palsy; Asthma exacerbation or reactive airway disease episodes in children and adults (TIV only)

Inadequate, but the epidemiologic evidence is “moderate” (9 Vx-AE)

Influenza: Seizures; GBS; LAIV-asthma/RAD (moderate null); Stroke, MI, all cause mortality (moderate decreased risk; only 1 study each)

MMR: Meningitis (moderate null)

Hepatitis B: First demyelinating event (moderate null);
Type 1 diabetes (moderate null)

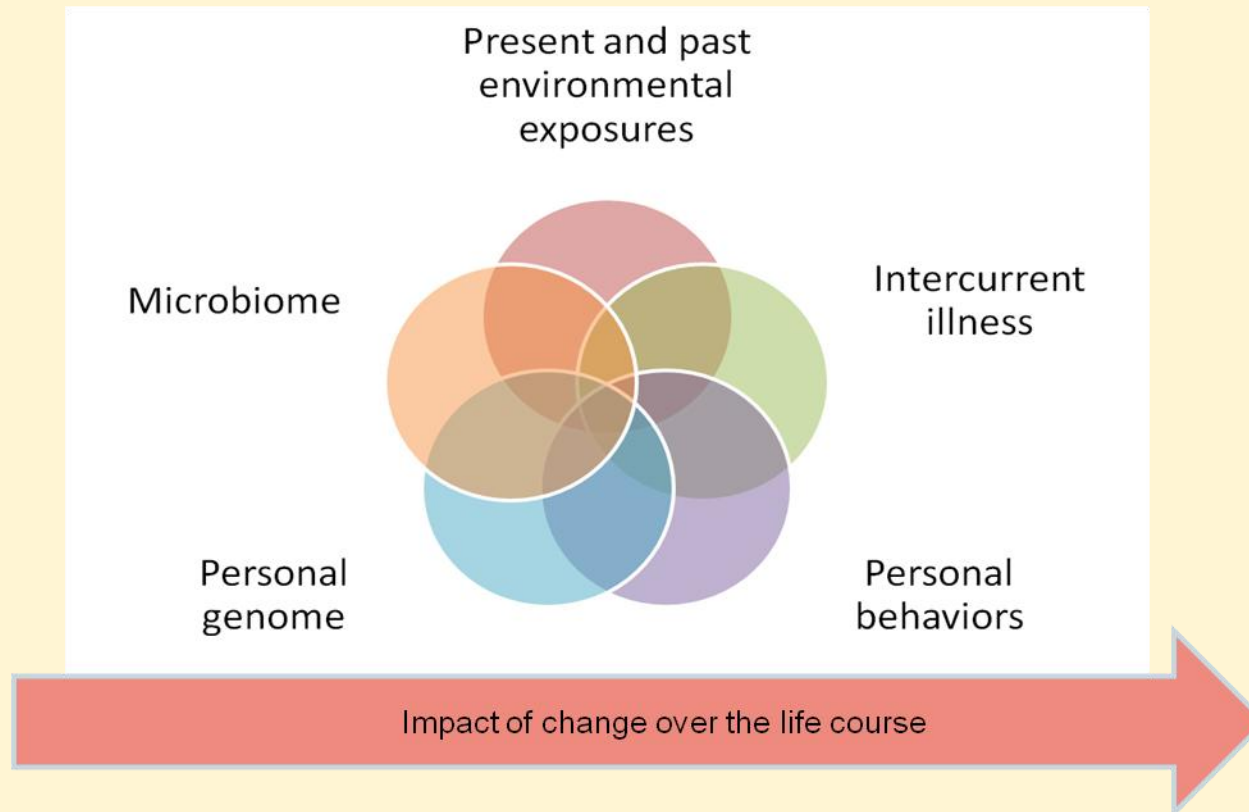
Inadequate, but the mechanistic evidence is “low-intermediate” (7 Vx-AE)

MMR: Chronic arthralgia and Chronic arthritis in women;
Hearing loss

Hepatitis B: Acute Disseminated EncephaloMyelitis,
First demyelinating event, vasculitis

Injection-related: Chronic Regional Pain Syndrome

Susceptibility – occurrence of disease often attributable to more than one cause



Susceptibility

- Invasive viral disease in immunocompromised individuals
- Immune mediated

Egg and gelatin allergic people

Predisposition to adverse effects of smallpox vaccines
(ICAM-1, CSF-3, IL-4)

Rechallenge

- Age and gender
- Metabolically &/or genetically vulnerable (SCN1A & DTP)

But note that some of these children have worse outcomes with the natural disease

We anticipate and hope that future studies will permit more causal conclusions to be reached

One of our goals was to be as transparent as possible about our process to provide a framework for future analysis